

**THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

CAREDX, INC. and THE BOARD OF)	
TRUSTEES OF THE LELAND)	
STANFORD JUNIOR UNIVERSITY,)	C.A. No. 19-567-CFC-CJB
)	CONSOLIDATED
Plaintiffs,)	
)	
v.)	
)	
NATERA, INC.,)	
)	
Defendant.)	
)	
)	
CAREDX, INC.,)	
)	
Plaintiff,)	
)	
v.)	
)	
EUROFINS VIRACOR, INC.,)	
)	
Defendant,)	
)	
and)	C.A. No. 19-1804-CFC-CJB
)	
THE BOARD OF TRUSTEES OF THE)	
LELAND STANFORD JUNIOR)	
UNIVERSITY,)	
)	
Nominal Defendant.)	

**PLAINTIFF CAREDX'S CONSOLIDATED OPPOSITION TO
DEFENDANTS' MOTION FOR SUMMARY JUDGMENT OF
INVALIDITY UNDER 35 U.S.C. § 101**

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I. NATURE AND STAGE OF THE PROCEEDINGS

On March 26, 2019, CareDx, Inc. (“CareDx”) filed a Complaint against Natera (D.I. 1)¹ alleging that Natera infringes U.S. Patent Nos. 8,703,652 (“the ’652 Patent”) and 9,845,497 (“the ’497 patent”). On March 12, 2020, CareDx added U.S. Patent Nos. 10,329,607 (“the ’607 patent”). D.I. 74-3.

On September 26, 2019, CareDx filed a Complaint against Eurofins Viracor, Inc. (“Eurofins”), alleging Eurofins infringes the ’652 Patent. D.I. 1, C.A. No. 19-1804.

Both parties challenged CareDx’s patents by motion to dismiss, alleging that the patents are invalid under 35 U.S.C. § 101 as a legal matter. The Court referred the motions to dismiss and other pretrial proceedings to Magistrate Judge Burke. Nov. 25, 2019 Oral Order. On February 10, 2020, Magistrate Judge Burke issued his Report and Recommendation that the motions to dismiss should be denied. D.I. 53 at 1-2. Magistrate Judge Burke concluded that, as a matter of law, the claims were not directed to a natural phenomenon and thus step one of the *Alice* test could not be satisfied. *Id.* at 5-9.

On April 21, 2020, this Court adopted the Report and Recommendation to deny the motion to dismiss in Eurofins (the parallel Natera motion had been found

¹ Unless otherwise noted, all docket item citations are to docket items in C.A. No. 19-567.

moot) but invited a pre-discovery summary judgment motion. D.I. 53, C.A. No. 19-1804. On April 30, 2020, the Court denied CareDx’s request for fact discovery. C1261 – C1265 (10:10-29:14).

Accordingly, the Defendants brought these early motions for summary judgment based on § 101. Because Defendants’ motions are so similar, CareDx files this single consolidated opposition addressing both motions.

II. SUMMARY OF THE ARGUMENT

Defendants argue the patents in suit are supposedly an improper attempt to patent a natural phenomenon. The alleged natural phenomenon is that the amount of donor cell-free DNA in a recipient over time correlates to potential organ rejection. Defendants’ motion defies law and logic.

The patents themselves criticize prior art attempts to measure the alleged natural phenomenon. They acknowledge that this phenomenon is long known in the prior art and is not the invention. The patents instead describe the inventions as a “universal approach to noninvasive detection of graft rejection in transplant patients which circumvents” the failings of the prior art measurement approaches.

In view of these undeniable facts, Defendants’ attempt to apply the two step *Alice* test to these patents fails resoundingly at both steps—and a failure at either step requires denial of these motions.

Step one asks whether the claimed inventions are directed to a natural phenomenon. This step, by Federal Circuit directive, must focus on the purported invention. The patents do not purport to have discovered, much less invented, the alleged natural phenomenon. The claimed advance expressly is a different and better way to *measure* the donor's cell-free DNA compared. The claims detail, with specifics, the improved measurement methods and the claims are very different from the prior art measurement approaches criticized in the patent.

Both *Rapid Litig.* and *Illumina* show why these motions should be denied. In both those cases, a natural phenomenon involving biological material centrally underlies the claims, yet the patents are not invalid because they purport to invent new laboratory methods of using the natural phenomenon. Defendants fail to meaningfully distinguish those cases.

Defendants' main cases are unenlightening because, in each one, the inventors purport to have discovered the natural phenomenon as a key part of the invention. In none of them does the patent acknowledge that the natural phenomenon is in the prior art and explain that it is an improvement on prior attempts to measure it.

Defendants' step two showing is equally off-base. Defendants contend that the natural phenomenon was known back in the 1990s. They also contend that, for the better part of a decade before the patents were sought, it was trivial to use

conventional measurement techniques to arrive at the organ transplant rejection inventions of the patents-in-suit. This is nonsense.

If this is so, how come nobody came up with these inventions for so many years? How come the research community instead broadly attempted the sub-optimal methods criticized in the patents? Why did a leading research group in the organ transplant field in **2008** conclude that the donor's cell-free (aka plasma free) DNA could not be accurately measured in the organ transplant context at the time of the invention: "It would be difficult to differentiate the origin of cell-free DNA in the plasma of heart transplant patients, making the use of plasma free DNA *impractical* for detection of organ rejection." See C208; see also C206 ("This phenomenon makes the use of plasma free DNA for the detection of organ rejection difficult and impractical."). These chronic prior art failures and deep doubts prove the patented measurement methods include an inventive advance far beyond the alleged natural phenomenon.

Moreover, Defendants' own evidence proves that the supposedly conventional techniques as applied to cell-free DNA were far from well-known. Defendants' expert, in his testimony in other cases involving related technology, admits that ordinary skilled artisans would have viewed the supposedly conventional techniques as uncertain and unsure for the claimed uses. Indeed, the record is replete with evidence that these techniques were anything but well-known for the

claimed uses in 2009. Indeed, Defendants’ expert testified that he did not know when these techniques were sensitive enough to work for organ rejection, except that they were good enough in 2009, when the filings for the patents-in-suit were made. C339:4-23.

Defendants’ attempt to perform a prior art analysis to try to prove conventionality would not pass muster to prove obviousness, which is a different and lower legal standard than conventionality. And the references Defendants cite are all clustered around 2009. If the technology were truly well-established by 2009, Defendants would not be applying only prior art from the same time-frame as the inventions. At a minimum, there are disputed factual issues that preclude summary judgment on the issue of conventionality and inventive advance.

Because Defendants fail to meet either step one or step two of the *Alice* test, and they must prove both, their summary judgment motions should be denied.

III. STATEMENT OF FACTS

The relevant facts are set forth below in the argument section.

IV. LEGAL STANDARD

Summary judgment is only appropriate when “the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law.” Fed. R. Civ. P. 56(a). The Court will “draw all reasonable inferences in favor of the nonmoving party, and it may not make credibility

determinations or weigh the evidence.” *Reeves v. Sanderson Plumbing Prods., Inc.*, 530 U.S. 133, 150 (2000). If there is material discovery yet to be taken, the motion should not be granted as set forth in Rule 56(d). Fed. R. Civ. P. 56(d).

V. ARGUMENT

A. The Claims Are Not Directed To A Natural Phenomenon

1. Step One Focuses On The *Purported* Invention

At step one of the *Alice/Mayo* test, “it is not enough to merely identify a patent-ineligible concept underlying the claim; we must determine whether that patent-ineligible concept is what the claim is ‘directed to.’” *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1050 (Fed. Cir. 2016); *Illumina, Inc. v. Ariosa Diagnostics, Inc.*, 952 F.3d 1367, 1371 (Fed. Cir. 2020). “The Supreme Court has cautioned that ‘too broad an interpretation of’ ineligible subject matter ‘could eviscerate patent law’ because ‘all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas.’” *Endo Pharm. Inc. v. Teva Pharm. USA, Inc.*, 919 F.3d 1347, 1352-53 (Fed. Cir. 2019) quoting *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 71 (2012); see *McRO, Inc. v. Bandai Namco Games Am., Inc.*, 837 F.3d 1299, 1313 (Fed. Cir. 2016) (“We have previously cautioned that courts ‘must be careful to avoid oversimplifying the claims’ by looking at them generally and failing to account for the specific requirements of the claims.”).

The focus of the “Alice/Mayo step one analysis [is] on what the inventors *did purport* to invent and what they claimed in their patent.” *Illumina*, 952 F.3d at 1374.² This is because the key to a proper step one analysis is the “claimed advance.” *Finjan, Inc. v. Blue Coat Sys., Inc.*, 879 F.3d 1299, 1303 (Fed. Cir. 2018) (“Starting at step one, we must first examine the ‘844 patent’s ‘claimed advance’ to determine whether the claims are directed to an abstract idea.”).

In evaluating what the inventors here *purport* to invent in their patents, the Court should not consider whether it suspects the purported invention is obvious or even whether it is tempted to conclude that it involves the obvious application of conventional techniques. Not only is obviousness law, with its many safeguards against the alluring temptation of hindsight, inapplicable, but even whether there is an inventive advance is not part of step one. *Illumina*, 952 F.3d at 1374 (“But while such considerations may be relevant to the inquiry under Alice/Mayo step two, or to other statutory considerations such as obviousness that are not at issue before us in this case, they do not impact the Alice/Mayo step one question whether the claims themselves are directed to a natural phenomenon.”).

To identify the purported invention and claimed advance, the Court should look to the specification. *See Enfish, LLC v. Microsoft Corp.*, 822 F.3d 1327, 1337

² Emphasis supplied unless otherwise noted.

(Fed. Cir. 2016) (relying on “specification’s teachings that the claimed invention achieves other benefits over conventional databases, such as increased flexibility, faster search times, and smaller memory requirements” in finding claims patentable at step one); *Core Wireless Licensing S.A.R.L. v. LG Elecs., Inc.*, 880 F.3d 1356, 1363 (Fed. Cir. 2018) (“The specification confirms that these claims disclose an improved user interface for electronic devices, particularly those with small screens [rather than an abstract idea].”); *Endo*, 919 F.3d at 1353 (relying on how the “specification predominantly describes the invention” in determining what it is directed to at step one).

2. The Patents Do Not Purport To Invent The Alleged Natural Phenomena And Instead The Claims Are Directed At The Prior Art Problem Of How To Measure The Donor Cell-Free DNA

Defendants assert that the natural phenomenon to which the patents are directed is the detection and correlation of donor DNA in an organ transplant recipient to monitor rejection. D.I. 62 at 12, C.A. No. 19-1804 (The natural phenomenon is that “donor-specific cfDNA from a transplanted organ circulates in the blood of a transplant recipient and can be correlated to transplant rejection.”); D.I. 101 at 14 (same).

The first fatal problem with Defendants’ motion is that they fail to grapple with the fact that the patents-in-suit explain that the alleged natural phenomenon is in the prior art and that prior art approaches to measuring that phenomenon were

limited. D27-D30. As a matter of logic, the purported invention cannot be what the patents themselves acknowledge is in the prior art – especially when the patents explain that their approach to measuring the phenomenon is new and better than past attempts.

As documented in the patents, prior attempts to measure donor cell-free DNA to monitor for organ rejection were limited and sub-optimal. It was not until the inventors recognized – when so many others in the prior art had not -- that the signal-to-noise problem could be resolved by a combination of polymorphism profile analysis and high-throughput sequencing techniques such as multiplex sequencing that the alleged natural phenomenon could be used more successfully.

The patents recognize that the detection of cell-free DNA in the blood plasma was known back to the 1940s and is not the putative invention. B12 at 6:57-59 (“Circulating, or cell-free, DNA was first detected in human blood plasma in 1948.”). The patents also acknowledge that studies dating back to the 1990s establish that “much of the circulating nucleic acids in blood arise from necrotic or apoptotic cells (Giacona, M. B., et al., *Pancreas*, 17, 89-97 (1998)) and greatly elevated levels of nucleic acids from apoptosis is observed in diseases such as cancer.” B12 at 6:61-66.

The patents explain that there were numerous attempts to devise laboratory testing methods that would be able to use the presence of donor cell-free DNA to

monitor for organ rejection (the alleged natural phenomenon) -- but they were limited. *See* B13 at 7:48-8:54. As the patents explain, in one set of attempts, the investigators attempted to invent a test that could be used for women organ transplant recipients when they received organs from male donors. In those cases, the male genetic-marker was thought to allow the test to distinguish between the female recipient's cell-free DNA and male donor's cell-free DNA. B13 at 8:22-26 ("While each of these studies demonstrates donor-DNA in bodily fluids for different solid organ transplants, they are all limited to the special case of females receiving organs from males and will not work for females receiving from females, males receiving from males, or males receiving from females."). Not only was this limited to female's receiving organ donations from males, but it underestimated the problem of microchimerism that polluted the results. B13 at 8:27-31 ("Further problems with this strategy arise from the prevalence of microchimerism in female patients where past male pregnancies or blood transfusions may lead to Y-chromosome specific signals from sources other than the transplanted organ.").

The patents identify prior art reports disclosing another weaker prior art strategy to leverage the alleged natural phenomenon using a measurement technique involving HLA, which is a protein. B13 at 8:34-39. After identifying the prior art reports, the patents explain that this measurement strategy is limited and sub-optimal as well. B13 at 8:39-43. ("[T]his strategy will also be limited by the

inability to distinguish HLA alleles between all donors and recipients, particularly for common HLA types, and the potential complication of microchimerism such as from blood transfusions.”).

In short, the patents themselves acknowledge that the alleged natural phenomenon (increased cell-free donor DNA in recipient blood may suggest organ rejection) was long known and explain with particulars how and why prior art attempts to measure the phenomenon were inadequate. Thus, the patents do not purport to have invented the alleged natural phenomenon because they acknowledge that it was long known before the invention and that the invention in these patents is improved measurement techniques.

The patents explain affirmatively that the putative invention and claimed advance is a patent-eligible new way to measure the cell-free DNA that is better than the prior art approaches:

[T]he invention provides a universal approach to noninvasive detection of graft rejection in transplant patients which circumvents the potential problems of microchimerism from DNA from other foreign sources and is general for all organ recipients without consideration of gender. In some embodiments, a genetic fingerprint is generated for the donor organ. This approach allows for a reliable identification of sequences arising solely from the organ transplantation that can be made in a manner that is independent of the genders of donor and recipient.

B13 at 8:45-54. This section of the patents is unambiguous that the purported invention and claimed advance is a new way to measure cell-free DNA that improves

on the prior art approaches that tried inadequately to measure the natural phenomenon.

3. The Claim Text Establishes, Consistent With The Specification, That The Purported Inventions Are Not The Natural Phenomenon

None of the challenged claims focuses on the alleged natural phenomenon as the invention. As explained by CareDx's expert, they each contain specific measurement methods that were never before applied to organ transplant rejection testing—even though the alleged natural phenomenon was long known in the prior art. *See* D18-D26. Especially when considered in light of the specification, the claims are directed to a novel human-devised measurement method, not the alleged natural phenomenon, which was acknowledged to be long known.

4. None Of Defendants' Cases Are Persuasive Because None Of The Invalidated Patents In Those Cases Identify The Natural Phenomenon As Old Nor Do They Purport To Improve Upon Prior Art Methods

Defendants rely upon a list of cases holding that patents that purport to discover a natural phenomenon and merely add trivial methods are patent ineligible. Those cases are distinct from this case in exactly what matters most for the step one test: What is the purported invention and claimed advance? Here, the purported invention and claimed advance is new methods for measuring cell-free DNA for transplant rejection that others had failed to devise, as established above. It is not

the alleged natural phenomenon, which it eschews as the invention by acknowledging it is in the prior art.

By contrast, two highly relevant cases are *Rapid Litig.* and *Illumina* cases. Those two cases show that even where a natural phenomenon involving biological material centrally underlies the claims, the patents are not invalid when they purport to invent new laboratory methods of using the natural phenomenon. And in both cases, the method steps were each alleged to be conventional such as freezing and unfreezing liver cells, but that did not mean the purported invention was directed to a natural phenomenon.

Defendants attempt to distinguish *Rapid Litig.* and *Illumina* by arguing that those cases involve methods that started with one natural substance and ended with another. They contend that, on the contrary, in this case the starting material is supposedly the same as the ending material. Defendants' distinction fails.

In both cases, the end product could be said to be the same as the starting product, and yet the claims were found to be patent eligible because step one was satisfied. In *Rapid Litig.*, 827 F.3d at 1046-47, the liver cells that could survive freezing and were the output of the claimed method were the same liver cells that were inputs into the process. Likewise, in *Illumina*, the Federal Circuit upheld the claims even though the accused infringer argued that the cell-free DNA that was separated out was the very same cell-free DNA that was the input into the method.

Illumina, 952 F.3d at 1369-70. Also, the measured cell free DNA in this case is different from the starting material in substantial ways.

5. The Law Of The Case Doctrine Applies

Under the law-of-the-case doctrine, “when a court decides upon a rule of law, that decision should continue to govern the same issues in subsequent stages in the same case.” *Christianson v. Colt Indus. Operating Corp.*, 486 U.S. 800, 816 (1988) (citation omitted). “This rule of practice promotes the finality and efficiency of the judicial process by protecting against the agitation of settled issues.” *Id.* (citation and quotation marks omitted).

Here, this Court adopted Magistrate Judge Burke’s Report and Recommendation on the legal question as to whether step one was satisfied. D.I. 53. The step one issue raised by this motion is the same issue faced by Magistrate Judge Burke. Defendants have not identified: (1) any case finding that step one could involve fact issues, (2) any meaningful difference in the record now as it relates to step one, or (3) any reason Magistrate Judge Burke’s analysis would be different on this motion.

In adopting the Report and Recommendation, this Court expressed agreement with Magistrate Judge Burke, finding that it was premature to invalidate the claims on § 101 grounds. D.I. 53, C.A. 19-1804 at 2.

There is nothing about Magistrate Judge Burke’s step one analysis that would change from the preliminary posture of a motion to dismiss to this early summary judgment motion. That analysis was based on the specifics of the patents’ intrinsic evidence. The law of the case doctrine thus applies. *Schneyder v. Smith*, 709 F. Supp. 2d 368, 384 (E.D. Pa. 2010) (“[A]lthough courts must address the evidence of record when deciding motions for summary judgment, applying this standard does not always create an exception to the law of the case doctrine. Rather, it depends on whether defendant has produced evidence in the motion for summary judgment that the ‘relevant facts are different’ from those considered by the court in the motion to dismiss.”) (citation omitted).

This Court also cited the Federal Circuit’s *Athena* decision and expressed doubt about the validity of the patents. *Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC*, 915 F.3d 743 (Fed. Cir. 2019), does not change the analysis at all. In *Athena*, the primary discovery described in the specification was the discovery of the natural law. *Id.* at 751 (concluding that “claims 7-9 are directed to a natural law because the claimed advance was only in the discovery of a natural law”). Here, the patents do *not* describe the alleged natural phenomenon as a new discovery, but instead tout their measurement method as an improvement over the prior art. This case is the opposite of *Athena*.

In *Athena*, the method used to observe the newly-discovered natural law was routine and not an improvement over the prior art. *Id.* (“The '820 patent thus describes the claimed invention principally as a discovery of a natural law, not as an improvement in the underlying immunoassay technology.”). Here, the methods used to measure the alleged natural phenomenon are specifically described as the “claimed advance” over flawed prior art methods. This, too, is the opposite.

The law of the case doctrine applies, and none of the exceptions apply.

6. Defendants Do Not Even Attempt To Prove Preemption

Preemption can be relevant to the step one test. *Endo*, 919 F.3d at 1354. Defendants do not allege preemption. How could they? Instead of pre-empting use of a natural law, the patents describe ways that the prior art actually used the natural phenomenon, although not as effectively. Indeed, Defendants do not deny that there are countless other ways that the natural phenomenon could be used other than the specific measurement methods of the claims. This confirms the claims are not directed to the natural law, but rather an improved measurement method, as confirmed by CareDx’s expert. *See* D26-D30.

In sum, step one is not satisfied, and the motion should be denied without more.

B. The Claims Encompass An Inventive Concept

Even if the Court were to conclude that the claims are directed to a natural phenomenon, and thus find it proper to move to step two, summary judgment of ineligibility is still unwarranted because the claims encompass an inventive concept, as explained by CareDx's expert. *See* D27-D85. Where claims do not broadly preempt related technologies, do not merely combine elements in a generic manner, and provide a particular solution to a problem in the art, an inventive concept is likely to exist. *See Amdocs (Israel) Ltd. v. Openet Telecom, Inc.*, 841 F.3d 1288, 1301 (Fed. Cir. 2016) (*Alice* step two satisfied where claim "narrowly drawn to not preempt any and all generic enhancement of data in a similar system, and does not merely combine the components in a generic manner, but instead purposefully arranges the components in a distributed architecture to achieve a technological solution to a technological problem specific to computer networks"). Defendants all but acknowledge that the patents-in-suit meet these criteria.

Defendants do not argue that there would be any preemption of the alleged natural phenomenon. Defendants' expert, Dr. Quackenbush, did not even opine on the topic because he did not feel qualified. *See* C392:5-15. The burden of proof and the burden of going forward is on Defendants and they failed to even attempt to meet it.

The patents-in-suit explain that the inventive concept is an improvement in the prior art measurement methods, as described above, relative to step one. Tellingly, Defendants never address the relevant disclosures in the specification. Having failed to address the very concept the patents identify as inventive, Defendants cannot show that there is no genuine issue of material fact as to inventive concept.

Additionally, CareDx identifies material discovery that it has not had an opportunity to pursue, under FRCP 56(d) through its accompanying declaration of Edward Reines, that further supports denial of these motions. This discovery pertains to the many challenges Defendants faced in attempting to design their own assays for detecting organ transplant rejection using cell-free DNA, Defendants' own patent filings and licensing practices, and technical publications from individuals affiliated with Defendants regarding the relevant technology.

CareDx expects that further discovery regarding these topics will contradict Defendants' position that the methods provided by the asserted patents were routine and conventional as of November 6, 2009. Consequently, Defendants' motions should be denied for a host of reasons, including that summary judgment is premature before fact discovery is complete. *See Miller v. Beneficial Mgmt. Corp.*, 977 F.2d 834, 845–46 (3d Cir. 1992) (holding that the district court erred in granting summary judgment because summary judgment was premature in the absence of

crucial discovery); *Doe v. Abington Friends Sch.*, 480 F.3d 252, 257-59 (3d Cir. 2007) (holding that district court prematurely granted summary judgment without allowing further discovery); *Metro. Life Ins. Co. v. Bancorp Servs., L.L.C.*, 527 F.3d 1330, 1337 n.3 (Fed. Cir. 2008) (noting that it is the “prevailing rule in all circuits” that summary judgment is inappropriate until there is an adequate opportunity to conduct discovery); C1267-C1275 (granting motion to defer summary judgment pursuant to FRCP 56(d) where summary judgment motions were filed prior to claim construction and deadline for fact discovery and expert reports).

1. The Claimed Measurement Methods Filled A Long Standing Gap In The Field And Were Not Routine And Conventional

According to Defendants, not only was the alleged natural phenomenon known back in the 1990s, all the techniques and concepts necessary to exploit that phenomenon as set forth in the invention were available and had been known for many years, if not decades, before the filing of the patents-in-suit. Dr. Quackenbush testified that the patents identify a 1998 publication by Lo that disclosed the alleged natural phenomenon and that “Lo recognized in 1998 that the concentration could be a marker for rejection and that it would correlate with increased levels of DNA corresponding to cell death.” C350:1-C351:11 (“they cite to a number of different references that established the presence of transplant donor DNA in a recipient cell-free DNA in a recipient, and point to, I believe, this [1998]

Lo paper stating that the correlation could be indicative. And I think they cite to other references as well.”).

Dr. Quackenbush also opines about how well-known all the laboratory techniques required for the invention supposedly were. According to Dr. Quackenbush, genotyping was available in 1995, nucleic acid amplification was available in 2000, and the necessary sequencing technology was available starting in the 1980s. *See* A43-A44, A54-55. Dr. Quackenbush asserts that “[m]ultiplex and high-throughput sequencing techniques, including sequencing-by-synthesis techniques, had been in use for more than a decade before the 2009 filing date of the Patents.” A55 ¶ 103.

All these techniques were not just known, Dr. Quackenbush says, but were actually part of the core competencies of the skilled artisan. A10-A11 ¶ 24. Yet, despite everything that was supposedly known long before 2009, there were no universally applicable tests for the life-saving application of detecting organ transplant rejection. Dr. Quackenbush, who prepared opinions on how routine and conventional the science supposedly was, and thoroughly researched the art, could not identify any such tests:

- Q.** As of 2009, were there any tests using cell-free DNA that were actually being used on patients?
- A.** I’d hesitate to speculate. There could have been investigative studies. I don’t know.

C411:5-9.

If the technologies for performing the claimed invention were so widely available and the science was so well-understood for so long, why were there no universal tests for organ transplant rejection prior to 2009? Why were prior artists pursuing other very different approaches as documented in the patent? Of course, the answer is that the technology was not thought of as routine and conventional by skilled artisans who perceived organ transplant testing as a daunting task. *See, e.g.* D51-D63. The amount of donor cell-free DNA in the recipients' blood is a small fraction. The background noise of the recipient's DNA can easily drown out the ability to detect the donor's DNA.

After a rigorous peer review process, the work related to the patents-in-suit was published in 2011 in the Proceedings of the National Academy of Sciences, one of the most prestigious science journals. C1005-C1010. If the methods in the patents-in-suit were nothing but the unsurprising application of routine and conventional methods, they never would have been published in that journal. *Id.*; D66-D67; *see also* C2128 (describing CareDx's work published in the proceedings of the National Academy of Sciences as a "landmark study.").

Ignoring facts such as these, Dr. Quackenbush and Defendants rely heavily on a passage in the specification stating that the "practice of the present invention employs, unless otherwise indicated, conventional techniques...which are within the

skill of the art.” D.I. 101 at 18 (citing B0012 at 5:36-48). Defendants casts this as an acknowledgment that the claimed inventions are nothing but routine and conventional methods even though the patents describe their measurement methods as inventive improvements over the prior art. *Id.*

The cited passage, however, is nothing more than a citation to some basic treatises disclosing techniques that are used universally across the biological sciences. *See* D66-D67. The passage, and the citation of treatises, is boilerplate that is reproduced verbatim in countless patent filings totally unrelated to the patents-in-suit going back more than a decade. *See, e.g.,* C1244-C1245 ¶ 17 (US20190112599); C1164 at 21:50-63 (U.S. Patent No. 10,655,173); C1186 ¶ 22 (US20120252063); C1226 ¶ 34 (US20180237845); C1115-C1116 at 8:58-9:4 (U.S. Patent No. 8,704,037); C1057 at 13:30-43 (U.S. Patent No. 8,053,627). Defendants’ heavy reliance on such boilerplate is weak; no law stands for the proposition that an invention is ineligible for patenting because it utilizes basic tools in a field.

Defendants also rely on passages in the patents documenting prior art techniques related to PCR, sequencing, and microarrays. *See* D.I. 101 at 20-25. Nowhere, however, do the patents state that these techniques are “conventional” for any purpose, let alone the unexplored task of analyzing cell-free DNA by high-throughput sequencing and digital PCR to detect organ transplant rejection. Quite

the contrary, with respect to the high-throughput sequencing and digital PCR techniques used in the claims, the patents' description of these methods frequently relies upon citation to publications and patent applications from shortly before the priority date. *See, e.g.*, B13 at 8:1-8; B16 at 14:55-67, B17 at 15:22-37, 15:57-60; B22 at 25:46-53.

The discussion of high-throughput sequencing in the patents encompasses roughly two and a half columns worth of detailed description regarding the specific design details and capabilities of high-throughput sequencing. *See* B17-18 at 15:1-17:39. If such techniques were so routine and conventional for the detection of organ transplant rejection, why would the patents include so much nuance and detail? A fair reading of the patents' description of high-throughput sequencing would not lead one to believe that high throughput sequencing was conventional, but rather that it was the subject of intense ongoing research and that its applications were being explored. *See* D49-D50. This "otherwise indicates" that this technology is not conventional.

While Defendants and Dr. Quackenbush pore over all the individual techniques the patents cite as being in the prior art, they studiously ignore the literature cited in the patent that addresses whether such technology could actually be used to detect organ transplant rejection. Such literature, as late as 2008,

presents a bleak outlook by flat out stating that the use of cell-free DNA to monitor organ rejection was impractical:

In conclusion, our findings suggested a high prevalence of chimeric DNA (in different ratios) in female recipient plasma. It would be difficult to differentiate the origin of cell free DNA in the plasma of heart transplant patients, making the use of plasma free DNA *impractical* for detection of organ rejection.

C208; *see also* C206 (“This phenomenon makes the use of plasma free DNA for the detection of organ rejection difficult and impractical.”).

The invention of the patents-in-suit resulted from the recognition for the first time by the inventors that a number of developing technologies could be applied in a novel way to the context of organ transplant, which was perceived as daunting and where others had come up only with sub-optimal approaches. As such, whether the claim steps are considered individually or as a whole, Defendants cannot meet its burden of showing that the claimed invention does not include an inventive concept.

2. Defendants’ Prior Art References Confirm That The Claims As A Whole Were Not Routine And Conventional

While Defendants devote substantial effort to addressing whether individual concepts used in the claims were routine and conventional, it spends far less time addressing the most salient question of whether the claims as a whole were routine and conventional. *See* D.I. 101 at 29-31.

Defendants’ argument regarding the claims as a whole consists solely of identifying a few prior art references that disclose approaches supposedly “close” to the claimed inventions of the patents-in-suit. *Id.* Defendants’ expert submits charts that list where “Claim Elements” are allegedly taught in Defendants’ prior art references. *See* A82-A100. Yet, the “Claim Elements” in Dr. Quackenbush’s charts are not actually claim elements, but rather generic concepts that Dr. Quackenbush formulated as proxies for the claim elements in an attempt to oversimplify the claims. *See* D35-D39. Dr. Quackenbush even admitted that “maybe the use of the term ‘claim element’ isn’t proper.”³ C321:21-23. His analysis “looks similar to an obviousness analysis under 35 U.S.C. § 103, except lacking an explanation of a reason to combine the limitations as claimed.” *Bascom Global Internet Servs., Inc. v. AT&T Mobility LLC*, 827 F.3d 1341, 1349-50 (Fed. Cir. 2016). It is precisely the type of deviant analysis the Federal Circuit has warned against in the context of U.S.C. § 101. *See id.*

Regardless, the references cited by Dr. Quackenbush and Defendants simply confirm that the patents-in-suit were not routine and conventional. Defendants rely

³ CareDx objects to Dr. Quackenbush’s opinions based on his gross oversimplification of the claims. Appendix A. This is an unreliable approach that does not satisfy the minimum standards for admissibility. *TiVo, Inc. v. EchoStar Commc’ns Corp.*, 516 F.3d 1290, 1311 (Fed. Cir. 2008) (limiting expert testimony on validity to opinions directly relating to the claims as construed).

on two primary references: a 2007 patent application by Cantor and a 2009 patent application by Lo. D.I. 101 at 29-30. These near contemporaneous patent applications claiming to disclose cutting edge technology are hardly the way to show that technology is conventional in 2009. *See* D67-D68.

Neither of Defendants' primary references disclose any experiments related to the analysis of cell-free DNA for detection of organ transplant rejection. At most, they include one-off speculation that the techniques used therein might be applicable in this context without explaining how. *See* B401, B1251. Defendants' expert admitted that none of his seven prior art references teach the claimed inventions and at most a couple speculate about it. C298:22-C299:10. ("I don't think any of them directly describe transplants. Some of them may have speculated about it."). Such speculation discloses a desire for a method that can address organ transplant rejection based on cell-free DNA, not evidence that such methods were routine and conventional. While Defendants cite five additional prior art references, not one of them pertains to any experiments regarding the use of cell-free DNA to detect organ transplant rejection. This fact belies any assertion that the claims as a whole were routine or conventional.

All seven of the prior art references relied upon by Defendants are dated 2007 or later, with three coming from 2009 and one even coming from 2010, which is *after* the 2009 priority date. *See* A88-A100 (relying on B428-B460). Defendants

reliance only on prior art that is heavily clustered around the priority date of the claimed inventions shows that the relevant techniques were not routine and conventional, but rather approaches that were new and developing. *See* D67-D68.

“Whether a particular technology is well-understood, routine, and conventional goes beyond what was simply known in the prior art. The mere fact that something is disclosed in a piece of prior art, for example, does not mean it was well-understood, routine, and conventional.” *Berkheimer v. HP Inc.*, 881 F.3d 1360, 1369 (Fed. Cir. 2018), *cert. denied*, 140 S. Ct. 911 (2020). Defendants’ reliance on references so close in time to the invention of the patents-in-suit ignores this rule and does not establish that the claimed techniques were routine and conventional. In any event, as explained by CareDx’s expert, the methods in Defendants’ prior art references are materially different from the claimed inventions. *See* D70-D85. This simply provides additional evidence that the claimed techniques were not routine and conventional.

3. The Individual Claim Elements Were Not Routine And Conventional In 2009

As noted above, the bulk of Defendants’ argument focuses not on the claims as a whole, as the law requires, but rather individual technical concepts. Notably, Defendants’ do not even consider the actual claim steps. Rather, Defendants reduce the claims across three patents-in-suit to four generic technical concepts and

argue that these concepts were individually routine and conventional. *See* D.I. 101 at 17-29.

This type of analysis proves little. As the Federal Circuit has explained, even where a claim is composed entirely of “generic” steps, it is nonetheless eligible for patenting if the combination supplies an inventive concept:

We agree with the district court that the limitations of the claims, taken individually, recite generic computer, network and Internet components, none of which is inventive by itself. BASCOM does not assert that it invented local computers, ISP servers, networks, network accounts, or filtering. Nor does the specification describe those elements as inventive.

However, we disagree with the district court’s analysis of the ordered combination of limitations. *In light of Mayo and Alice, it is of course now standard for a § 101 inquiry to consider whether various claim elements simply recite “well-understood, routine, conventional activities.” The district court’s analysis in this case, however, looks similar to an obviousness analysis under 35 U.S. C. § 103, except lacking an explanation of a reason to combine the limitations as claimed. The inventive concept inquiry requires more than recognizing that each claim element, by itself, was known in the art.* As is the case here, an inventive concept can be found in the nonconventional and non-generic arrangement of known, conventional pieces.

Bascom, 827 F.3d at 1349-50 (citation omitted). As documented above, there is an inventive concept that improves the measurement method compared to the prior art approaches.

Defendants’ argument that certain concepts were routine and conventional in the 2009 time frame also fails as a factual matter. “The question of whether a claim

element or combination of elements is well-understood, routine and conventional to a skilled artisan in the relevant field is a question of fact.” *Berkheimer*, 881 F.3d at 1368.

As shown below, there is overwhelming evidence that the concepts Defendants identify were not routine and conventional in the 2009 time frame in the context of cell-free DNA. Incredibly, Defendants’ own expert has given testimony in ongoing cases that pertain to the use of next generation sequencing for analyzing cell-free DNA that completely undermines Defendants’ positions in this case. This contradictory testimony along with the documentary evidence and opinions of CareDx’s expert at a minimum establishes that summary judgment is unwarranted.

**a. Obtaining Or Providing A Biological Sample
Containing Cell-Free Nucleic Acids From A
Transplant Recipient**

Citing a portion of the specification stating that to “obtain a blood sample, any technique known in the art may be used,” Defendants contend that there is “no evidence” that the claim steps related to obtaining a sample are not routine and conventional. D.I. 101 at 22. Defendants’ reliance on the specification’s disclosure regarding the process of merely obtaining blood, however, is irrelevant because the claimed methods pertain not to the analysis of raw blood, but to cell-free DNA within blood. On this issue, Defendants are silent. To meet its burden,

Defendants must put forth affirmative evidence that this concept was routine and conventional, not merely assert that there is “no evidence” to the contrary.

In fact, Defendants cannot prove that this concept was routine and conventional in view of the testimony and opinions of its own expert. Dr. Quackenbush testified that prior art approaches for cellular DNA are unreliable as predictors for what will work with cell-free DNA: “just because a technique is designed for cellular DNA does not necessarily make it well suited to cell-free DNA – a fundamentally different sample type.” C513-C514 ¶ 24. According to Dr. Quackenbush, “different sample types can have different challenges in different applications. So every measurement you make faces some potential challenges, depending on what – you know, what you’re measuring and what you’re trying to do.” C487:21-C488:1; *see also, e.g.*, C11-C12 ¶¶ 26-28; C158-C159 ¶¶ 202-03; C162 ¶ 210; C163-C165 ¶¶ 213-15; C517 ¶ 33; C838:4-C839:7; C839:18-C840:7; C841:6-C842:18; C843:1-C844:12; C845:7-13; C846:14-C847:21; C702:11-C703:3.

Contamination, for instance, is a special concern that applies in the organ transplant setting. Technical literature from as recently as 2019 establishes that it was not routine and conventional to prepare cfDNA samples from blood to monitor organ transplant because “[f]ailure to exert the needed pre-analytical precautions in

cfDNA DF testing will result in underestimation of DF and, *potentially, false negative reporting of rejection risk.*” C539.

Dr. Quackenbush, for his part, recently opined on the preparation of DNA from fetal cells in blood, explaining that “while improvements have been made for the isolation and enrichment of fetal cells, *it is still difficult to get many fetal blood cells.* There may not be enough to reliably determine anomalies of the fetal karyotype or assay for other abnormalities. Furthermore, most techniques are *time consuming, require high-inputs of labor, and are difficult to implement for a high throughput fashion.*” C158-C159 ¶ 203 (citing to U.S. 2004/0137470 A1 (“Dhallan”)). According to Dr. Quackenbush, the use of “cell-free DNA would have *enhanced*” such problems. See C162 ¶ 210.

Thus, taking Defendants’ expert at his word, even the supposedly simple process of obtaining a sample cannot be deemed routine and conventional in the 2009 time frame.

b. High Throughput/Multiplex Sequencing

Relying largely on the opinion testimony of its expert, Defendants contend that the claimed sequencing techniques were “routine and conventional” because, as of 2009, various sequencing platforms were commercially available. D.I. 101 at 24. The claimed invention, however, specifically uses such platforms for monitoring organ transplant rejection via cell-free DNA analysis. The mere fact

that a sequencing device was commercially available for relatively straightforward applications does not establish that it was routine and conventional for this purpose in 2009. In the 2009 time frame, high throughput sequencing was undergoing rapid development and understood to have drawbacks, and researchers did not understand the full scope of how these platforms may be applied, as confirmed by CareDx's expert. *See generally* D47-D63.

A 2009 study highlighted some of the issues encountered with next generation sequencing, noting in particular "biases in sample library generation, difficulties mapping short reads, variation in sequence coverage depth of unique and repetitive elements, difficulties detecting indels with short reads, the systematic errors of the NGS technologies and the impact of all these features on variant calling accuracy." C610. Based on these complications, the authors concluded that "[a]lthough recent improvements in the NGS platforms, such as paired end and longer reads, will mitigate these issues, all aspects of the NGS platforms, laboratory methods, sequence alignment tools, and base calling algorithms partially contribute to the problems and, therefore, need to be simultaneously optimized." C611. In other words, as of 2009, next generation sequencing was not routine and conventional, especially for use with cell-free DNA. *See* D48-D50.

When one considers the particular purposes for which sequencing is used in the claims (detection of polymorphisms in cell-free DNA), it becomes even clearer

that high throughput sequencing was by no means routine and conventional. For example, a 2019 publication notes the recent advancements provided by next generation sequencing in this context and characterizes them as “new methods:”

More recently, advanced technologies such as multiplexed high-fidelity amplification combined with allele-specific real-time quantitative PCR and newer versions of next generation sequencing (NGS) have been leveraged. These *new methods* improve sensitivity by interrogating a large multiplicity of highly informative single nucleotide polymorphism (SNP) sites, empowering prospective clinical studies that correlate cfDNA DF with biopsy-documented transplant rejection grade in well-defined patient populations of heart, kidney, liver and lung transplant recipients.”

C524. The authors note that even today there are issues with next generation sequencing that limit its applicability when one targets particular genomic regions: “Using NGS, we previously demonstrated a strong positive correlation between elevated DF and both ACR and AMR in pediatric and adult heart transplant patients. However, *standard targeted NGS is significantly limited by its cost, turnaround time (TAT), and level of sensitivity imposed by background noise.*” *Id.*

Multiple researchers have made similar comments regarding the state of the art of high throughput sequencing in the relevant time frame. *See, e.g.*, B240 (“Although considerable work lies ahead to implement NGS into clinical diagnostics, the potential applications are exciting and numerous.”), B325, B331 (“The accuracy of next-generation sequencers is improving, but users generally rely

on relatively high redundancy of sequence coverage to determine reliably the sequence of a region, particularly of that containing a polymorphism.”); D60-D61.

Defendants and Dr. Quackenbush attempt to gloss over this by pointing out that certain sequencing platforms were commercially available in 2009, such as the platform sold by the Helicos company, for which Dr. Quackenbush served as a scientific advisory board member. If anything, the Helicos example illustrates how high throughput sequencing was not routine and conventional in the 2009 time frame even though certain platforms were known and even commercially available. *See* D56-D58.

At deposition, Dr. Quackenbush was unable to identify a single individual outside of Helicos who was able to successfully use the Helicos system, even though he was on the scientific advisory board of the company. C234:17-20. He admitted that he had never actually done any direct experiments running a Helicos instrument. C242:5-12. In Helicos’ March 2012 Form 10-K, the company characterized the state of the art of next generation sequencing as far from routine and conventional:

Nevertheless, as next generation sequencing technologies continue to improve the speed and reduce the per base cost of DNA sequencing, *these instruments continue to be limited by their detection sensitivity*, thereby requiring DNA amplification to obtain sufficient material to adequately read the sequence. As with Sanger-based sequencing technologies, this requirement for amplification adds to the cost and complexity of these sequencing methods, and presents limits on the scalability of sample preparation and may limit

the accuracy of the data produced. *Moreover, many NGS technologies appear to possess biases and are hampered by their lack of absolute quantitative accuracy which may limit their applicability to the broader genetic analysis space. Additionally, the practical application of sequence data for molecular diagnostics is still heavily burdened by the costs associated with NGS sample preparation workflows.*

C1284; *see* C270:20-C271:8 (“[T]hese technologies continue to be limited by their sensitivity to the need for amplification or cloning to obtain enough DNA or RNA from a sample for their instruments to adequately read the sequence”); *see also* D56-D58.

At deposition, Dr. Quackenbush was asked point blank whether the skilled artisan could use the Helicos platform to carry out the claimed invention of the patents-in-suit. His answer was the exact opposite of what one would have expected had the platform—which he helped develop—truly been routine and conventional for this purpose:

- Q.** Could a person of ordinary skill in the art in 2009 perform the sequencing necessary for the claimed inventions of the patents-in-suit using the current Helicos system that was available at the time, according to you?
- A.** So if we look at just performing sequencing, the instrument itself could generate sequence data. I -- and one could quantify molecules. I can't speak to whether or not one could do -- yeah, you started talking about performance characteristics. *Having no experience with generating data of the form described in the patents-in-suit, I can't speak to whether or not this instrument per se could have done that.*

C246:6-20; *see also* C894:7-13; C919:9-24. When asked when it became conventional to genotype to obtain a SNP profile, Dr. Quackenbush could not say:

Q. Yeah. No, I'm not asking you that. I'm asking you: When did it become conventional technology?

A. *So I couldn't tell you exactly.* You know, is it widely used? By 2009, it certainly was. I don't know when it would transition.

C336:2-7.

Curiously, Dr. Quackenbush also cites a publication from 2010 to support his opinion that skilled artisans routinely used high-throughput sequencing to detect SNPs in samples. A59-A60 ¶ 110. This publication, however, states that “[h]igh error rates of NGS technologies present *a challenge* for the accurate detection of genetic variants.” B350. Again, Dr. Quackenbush's own examples undermine his opinions and show that the high throughput sequencing was not routine and conventional in the context of the approach of the claimed invention.

c. Digital PCR

Claim element 1(d) of the '497 patent recites the use of digital PCR as an alternative to sequencing. Natera's own scientists have acknowledged that this was not routine and conventional in the relevant time frame. In 2008, only a year before the priority date of the asserted patents, Bernhard Zimmermann, Natera's future Vice President of R&D, published on the use of digital PCR for the testing of fetal

abnormalities using cell-free DNA. He concluded it was “too early” to assess whether digital PCR could be used diagnostically:

As digital PCR relies on statistical analysis and a series of algorithms indicating probability that a fetus is normal or affected, the question arises whether this method will be relegated for use as a screening tool or whether it will indeed pass the necessary scientific and regulatory hurdles permitting it to be used diagnostically. *As to date, only two potential proof-of-principle studies have been performed, it is too early to answer these questions.*

C601. This alone negates any suggestion by Natera that digital PCR would have been routine and conventional for the assessment of organ transplant rejection through the analysis of cell-free DNA.

d. Selective Amplification By PCR Of At Least 1,000 Single Nucleotide Polymorphisms In Cell-Free DNA

All the claims of the '607 patent require that one perform “selective amplification” of “at least 1,000 single nucleotide polymorphisms” by PCR. Rather than address this element directly, both Defendants and their expert, Dr. Quackenbush, group this element into a genericized “genotyping” step. *See* D.I. 101 at 22-23; A43-A46 ¶¶ 82-87. As CareDx’s expert explains, however, this amplification step is a process unto its own and cannot simply be regarded as part of a generic “genotyping.” D40. On the current record, and as confirmed by CareDx’s expert, Defendants cannot show that the selective amplification process was routine and conventional in 2009. *See* D39-D50.

Defendants’ expert claims in this case that “PCR, including selective amplification, was a well-understood, routine and conventional method for genotyping by 2009.” A43 ¶ 82. According to Dr. Quackenbush, this was known by 2000. A44 ¶ 83. This testimony should be taken with a grain of salt, however, in view of Dr. Quackenbush’s testimony from just a few months ago in another case on behalf of Defendants.

There, he provided detailed testimony that selective amplification of cell-free DNA by PCR was anything but routine and conventional. As Dr. Quackenbush explained, “a person of ordinary skill in the art would have expected it to be difficult to reliably amplify cell-free DNA in a manner that would render the amplification product representative of the intact [] genome.” C163 ¶ 213. This, he explained, was in part because “the majority of the available high-throughput sequencing technologies require polymerase chain reaction (PCR) and are subject to the *substantial bias that is inherent* to the PCR process.” C163-C164 ¶ 214 (citing C1878-C1884); *see also* C132 ¶ 151; C133-C135 ¶¶ 153-58; C137-C142 ¶¶ 161-69; C150-C151 ¶¶ 185-86; C162 ¶ 210; C163-C163 ¶¶ 213-15; C937:10-19. This inherent bias would affect the selective amplification of SNPs as well.

Likewise, in this case, in connection with Natera’s patent infringement counterclaims against CareDx, Dr. Quackenbush submitted a declaration defending the eligibility under § 101 of Natera’s U.S. Patent No. 10,526,658 (the “’658

patent”), which pertains to selective amplification. There, Dr. Quackenbush described the challenges of amplification of low abundance target sequences:

[W]hen multiple pair [of primers] are added to the same PCR reaction, ***non-target amplification products may be generated***, such as amplified primer dimers. The risk of generating such products increases as the number of primers increases. These non-target amplicons ***significantly limit the use of the amplified products for further analysis and/or assays***. Thus, improved methods are needed to reduce the formation of non-target amplicons during multiplex PCR.”

C577 ¶ 19 *quoting* ’658 Patent; C579 ¶ 22 (“[T]hese undesirable primer interactions, such as those resulting from allelic bias or primer dimers for example, increase as the number of target loci, and corresponding primer pairs are introduced into an amplification mixture.”).

Dr. Quackenbush explained that these problems were “longstanding” and that scientists had “struggled with the problem of undesirable interactions of primers, such as due to allelic bias, primer dimers and other issues – particularly in multiplex amplification reactions involving numerous target loci (and corresponding primer pairs) and in multiplex amplification reactions involving small amounts of target DNA in a sample.” C580 ¶ 24. Consequently, Dr. Quackenbush explained, “there was great interest in the field of nucleic acid analysis in developing methods to amplify DNA while avoiding undesirable or unintended interactions of amplification primers and undesirable or unintended effects such as allele bias,

particularly in samples containing small amounts of DNA or large numbers of target loci.” C581 ¶ 26.

If Dr. Quackenbush’s testimony is not clear enough, one can look further to the testimony of Natera’s scientists. In 2008, only a year before the priority date of the asserted patents, Natera’s future Vice President of R&D reported that “the establishment of multiplexed reactions is generally *a major challenge* and this is *not possible for SNP-based approaches*.” C600.

Attempting to nonetheless suggest that the state of the art was more advanced than it actually was, Dr. Quackenbush points to another commercial product, the RDT 1000. Dr. Quackenbush contends that the “RDT 1000 from the company RainDance Technologies combined ‘targeted sequencing’ by PCR of ‘hundreds to, thousands of genomic loci.’” A44-A45 ¶ 85. But in 2009, the RDT 1000 product was merely a *beta* product, a point Dr. Quackenbush confirmed during deposition. C278:12-19. Given that the RDT1000 was a beta product that was in testing in the 2009 time frame, it could hardly have been routine and conventional to use this instrument for selective amplification of DNA, much less in the context of cell-free DNA. See D45-D47; D52-D53. Like the Helicos product relied upon by Dr. Quackenbush, the RDT 1000 product undermines any contention that selective amplification of at least 1,000 SNPs was routine and conventional in 2009.

e. Quantification

While Defendants contend that the quantification steps in the claims were routine and conventional, the testimony of Defendants' expert again confirms that summary judgment is inappropriate. *See* D63-D65.

In support of his argument, Dr. Quackenbush cites a 2009 publication by Sampson and Zhao. A70-A71. That publication, however, describes a "new test" that was "recently developed" to use a set of SNPs to determine whether a specific individual contributed to a mixture of DNA, in an attempt to address the known biases inherent to PCR. B361. A report of a "recently developed" "new test" at the priority date of the patents-in-suit does not establish that something was routine and conventional, but rather the exact opposite.

Dr. Quackenbush's prior testimony on behalf of Natera undermines his position even further, particularly with regard to claims that call for amplification of the cell-free DNA. According to Dr. Quackenbush, a POSA as of 2009 would have understood that a PCR amplification would lead to distortion that would impact one's ability to quantify alleles. C138-C139 ¶ 164. According to Dr. Quackenbush, "amplification methods in the relevant timeframe amplified certain sequences preferentially to others, and rarely in ways that could be determined precisely in advance," such that one would not have been able to reliably calculate allelic ratios between individuals. C135 ¶ 158; *see also* C132 ¶ 151; C133-C135

¶¶ 153-58. Dr. Quackenbush thus explained that while available techniques might be able to make SNP presence/absence calls from amplified DNA, using this technique to accurately measure quantitative ratios of heterozygous SNPs would have proven much more difficult. *Id.*; *see also* C939:11-C940:17; C92-C93 ¶ 59; C137-C142 ¶¶ 161-69; C150-C151 ¶¶ 185-86; C156 ¶ 196; C157 ¶ 198-99; C162 ¶ 210; C163-C165 ¶¶ 213-15; C167-C169 ¶¶ 220-23; C841:6-C842:18; C845:7-13; C846:14-C847:21; C937:10-19.

Even as of 2018, researchers continued to note challenges associated with quantifying cell-free DNA:

[L]imitations of several methods for ddcfDNA quantification *impede clinical implementation of these assays*. While some ddcfDNA quantification techniques based on amplification of chromosome Y associated genes are only suitable in gender-mismatched transplantation settings, other universal techniques based on whole genome shotgun sequencing to quantify donor specific single nucleotide polymorphisms (SNPs) are *time consuming, require a complex bio-informatical analysis and long turnaround times*.

C620.

f. Defendants' Prosecution History Argument Further Undermines Its Position

Defendants assert that during prosecution the patentees submitted a declaration describing the use of the claimed invention by commercially available techniques. *See* D.I. 101 at 28-29; A51-A52. According to Defendants, this is an admission by the patentee that the claimed techniques were routine and

conventional. Defendants' reliance on the existence of certain commercial products, however, suffers from the same defects as Defendants' reliance on products like the Helicos sequencer and RDT 1000. *See* D62-D63.

Indeed, the genotyping step of the experiments was performed using the Illumina Omni1-Quad BeadChip array. B261. This was a new and advanced array product in 2009. *See* D62-D63. Dr. Quackenbush wrongly states that it was available in 2002. A52. Likewise, the sequencing part of the experiment was performed using a Solexa Genome Analyzer. B261. This instrument was released as a beta product just a few years before the priority date; only 13 instruments were available worldwide as of 2006,⁴ and it was not until a few years later that the researchers began applying this instrument to cell-free DNA in the context of non-invasive prenatal testing. *See* C1431; D55-D57. The declaration

⁴ The declaration provides no information regarding the specifics of the library preparation kit used and whether it corresponds to a technique that was available in 2009.

thus exemplifies the use of the newest technology available in 2009 in a rapidly developing field, not old techniques that had become routine and conventional.⁵

VI. CONCLUSION

For the foregoing reasons, Natera's motion should be denied.

⁵ Defendants also devote an entire section of their briefs to an argument that counsel for CareDx admitted the claim steps were routine and conventional. *See* D.I. 101 at 29. The very most that counsel for CareDx confirmed, however, was that “we have not introduced a whole new concept that never was known before to science in any way on a per word basis.” *Id.* Defendants’ need to rely on a statement about concepts never known to science “in any way on a per word basis” underscores the weakness of their overall position.

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Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

I hereby certify that this brief has been prepared in Times New Roman 14-point typeface using Microsoft Word, and contains 9,879 words as determined by the Word Count feature of Microsoft Word.

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